*Pharmacology Biochemistry & Behavior*, Vol. 15, pp. 485–488, 1981, Printed in the U.S.A.

# Low Dose Cocaine Self-Administration by Naive Rats: Effects of Body Weight and a Fixed-Time One Minute Food Delivery Schedule

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Received 12 May 1981

PAPASAVA, M., T. P. S. OEI AND G. SINGER. *Low dose cocaine self-administration by naive rats: Effects of body weight and a fixed-time one minute food delivery schedule.* PHARMAC. BIOCHEM. BEHAV. 15(3) 485–488, 1981.—The self-administration rates of four groups of eight rats for low dose cocaine (0.1 mg/kg infusion) under free feeding and 80% body weight conditions, with and without a fixed time 1 min (FT-1) food delivery schedule, were compared with those of saline reinforced animals under the same conditions. Results indicated that (1) overall, self-administration rates were significantly greater for cocaine reinforced animals, (2) significantly higher rates of cocaine self-administration occurred in body weight reduced rats and (3) the operation of FT-1 schedule neither significantly enhanced or inhibited drug intake. In the second experiment, schedule and no schedule conditions were reversed for the sixteen 80% body weight, cocaine reinforced rats. Results showed that reversing schedule and no schedule conditions produced no significant change in drug intake. It was concluded that low dose cocaine self-administration is significantly amplified by body weight reduction.

Schedule Cocaine Self-administration Body weight

THE schedule-induced self-injection (SISI) procedure first reported by Lang *et al.* [7] has recently been utilized to induce self-administration of a variety of drugs by naive rats. These drugs have included heroin [8,10], methadone [10], nicotine [7], ethanol [9], and d-amphetamine [13].

Within the SISI paradigm, it has been demonstrated that the type of drug, the nutritional state of the animal and the operation of a fixed time one minute (FT-1) food pellet delivery schedule, either independently or via interactions, may influence the rate of self-administration. These findings have led to the suggestion that drugs may be classified according to the interaction of factors necessary to initiate self-administration [5]. Thus far, three types of interactions have been identified. These are (1) where self-administration by rats is acquired at 80% body weight with no schedule operating, but is considerably enhanced in the presence of a schedule (alcohol [9] and heroin [8,10]), (2) where self-administration is acquired only by animals at 80% body weight in the presence of an FT-1 schedule (nicotine [7] and methadone [10]), and (3) where self-administration is acquired only by 80% body weight animals and is inhibited by the operation of the schedule (amphetamine [13]).

Several investigations have now established that intravenous infusions of cocaine are positively reinforcing in both rats [4, 11, 12] and monkeys [1, 3, 6] under a variety of experimental conditions. For rats, the findings indicate that optimal responding occurs within a dose range of 0.5 and 3 mg/kg, with little or no responding occurring at doses below 0.25 mg/kg [11,12]. In a recent report, however, food deprived rats self-administered high levels of cocaine at a dose of 0.1 mg/kg [2]. These latter results would seem to indicate that the threshold for cocaine self-administration by rats is considerably lower under conditions of food deprivation.

The objective of the present experiments was to examine low dose cocaine self-administration within the SISI paradigm.

## EXPERIMENT 1: SELF-ADMINISTRATION OF COCAINE AT 100% AND 80% BODY WEIGHT WITH AND WITHOUT AN FT-1 FOOD DELIVERY SCHEDULE

In this experiment, the level of cocaine reinforced self-injection at 100%, 80% body weight and 100%, 80% body weight under an FT-1 food delivery schedule was compared with saline reinforced animals under the same conditions.

### METHOD

*Animals*

Sixty-four naive male, Wistar albino rats, weighing approximately 400 g were used. The animals were housed in-

dividually in a temperature controlled room with a 12 hour light/dark cycle. Food and water were available ad lib. In experiments where animals were required at 80% of their body weight, these were reduced prior to surgery and then maintained at that weight, with water available ad lib.

*Apparatus*

The experimental chamber was a modified operant box (35×32×32 cm) with a bar and food pellet dispensing unit attached to one wall. The bar was situated 5 cm and the pellet dispensing unit 3 cm from the grid floor. The bar, when triggered, operated a syringe infusion pump (Sage Instruments, Model 341) which delivered 0.07 ml of cocaine or saline. A timing device set for a fixed interval of 5 sec was incorporated into the drug delivery system such that any bar presses by the animal during this period produced no programmed consequences. The number of infusions and bar presses during the experimental session were recorded on a cumulative recorder. In experiments when an FT-1 schedule was operating, the pellet dispenser unit delivered 45 mg Noyes food pellets non-contingently at the rate of one pellet per min.

*Drugs*

Solutions of cocaine hydrochloride (Macfarlan Smith Ltd., Edinburgh) were prepared for intravenous administration prior to each experimental session by dissolving cocaine in 0.9% sterile saline at a dose of 0.1 mg/kg infusion. The anaesthetic used for the surgery consisted of a combination of pentobarbital sodium and the chloral hydrate. The solution was injected intraperitoneally.

*Procedure*

All animals were weighed, anaesthetized and cannulae of SP 28 polythene tubing were implanted into the jugular vein. The cannulae were maintained in position by leather jackets worn by each animal. The cannulae were connected to a flexible swivel system which allowed animals relatively unrestricted movement. Following a three day recovery period from surgery, the animals were weighed and placed in the experimental chamber for 10 consecutive 1 hour testing sessions, at the same time each day. Each experimental session commenced by priming the animal with an initial infusion of cocaine or saline depending upon the experimental condition.

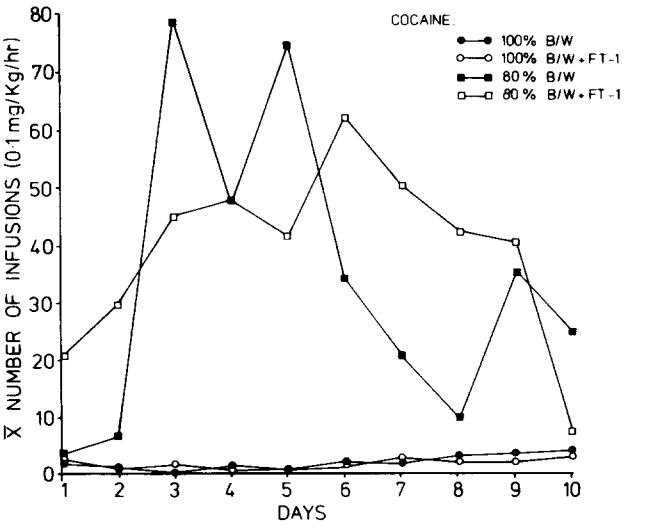


FIG. 1. Mean number of cocaine infusions during each 1 hour test period for each body weight/schedule group.

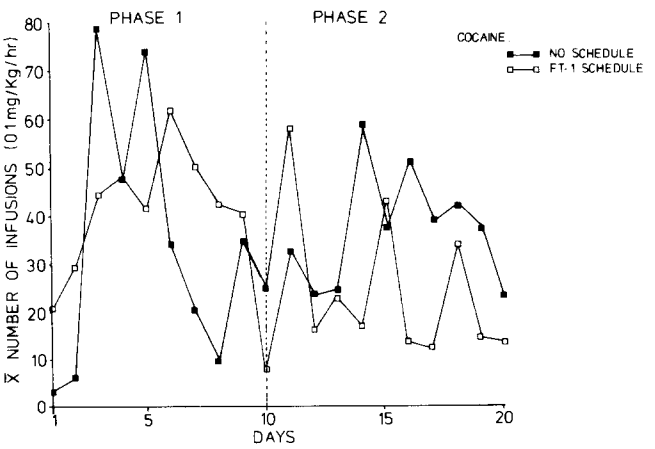


FIG. 2. Mean number of cocaine infusions during each 1 hour test period for each schedule group.

## RESULTS AND DISCUSSION

The mean number of infusions over the 10 day period for the four cocaine groups are presented in Fig 1.

A four way analysis of variance (ANOVA) with one repeated measure was applied to the data in order to determine main effects for drug conditions, body weight conditions, schedule conditions and days, and interactions between them.

Significant main effects were found between the rate of cocaine and saline infusions, $F(1,56)=8.450$, $p<0.05$, and between 80% and 100% body weight conditions $F(1,56)=9.571$, $p<0.05$. There was no significant difference between the infusion rates of animals in the schedule and no schedule conditions, which suggests that for cocaine self-administration, an FT-1 schedule is not an important factor. A significant interaction was found between the infusion rates of animals in the drug and body weight conditions, $F(1,56)=8.312$, $p<0.05$, suggesting that 80% body weight rats self-injecting cocaine had the highest rate of infusions (see Fig. 1).

A significant main effect was found over days, $F(9,504)=2.598$, $p<0.05$, and there were also significant interactions between the infusion rates of animals in the drug conditions over days, $F(9,504)=2.882$, $p<0.05$; body weight conditions over days, $F(9,504)=2.882$, $p<0.05$, and the three way interaction of drug, body weight and days, $F(9,504)=2.726$, $p<0.05$, suggesting that 80% body weight animals self-injecting cocaine had significantly greater rates of infusions over days than animals in any other condition (see Fig. 1).

In summary, irrespective of whether or not an FT-1 food delivery schedule was operating, 80% body weight animals in

the cocaine conditions had significantly higher rates of infusions over the 10 day period than animals in any other condition. The infusion rates of all other groups were very low.

The results obtained from the present experiment demonstrate that the operation of an FT-1 food delivery schedule does not significantly influence the level of cocaine self-administration. This finding, which was the same for both free feeding and reduced body weight rats, constitutes a pattern of self-administration which is dissimilar to any pattern observed thus far within the SISI paradigm [7, 8, 9, 10, 13].

## EXPERIMENT 2: REVERSAL OF SCHEDULE AND NO SCHEDULE CONDITIONS

In the previous experiment, it was established that the operation of an FT-1 schedule did not significantly affect rates of cocaine self-administration, and this finding was not consistent with the results of previous investigations (especially Takahashi *et al.* [13]). The objective of the present experiment was to determine whether or not the reversal of scheduled conditions for 80% body weight animals would alter rates of cocaine self-administration.

### METHOD

*Procedure*

Apparatus and procedure were identical to that in Experiment 1. In this experiment, the sixteen 80% body weight animals which had self-administered cocaine in the first experiment were tested for a further 10 consecutive days for 1 hour per day at the same time as previously. During this period, however, the 8 animals which had self-administered cocaine in the presence of an FT-1 schedule had the schedule removed, whilst the 8 animals previously self-administering in the absence of an FT-1 schedule had the schedule operating. As in Experiment 1, each experimental session commenced with a non-contingent infusion of cocaine.

### RESULTS AND DISCUSSION

The mean number of infusions for each group of animals over each period of 10 days is presented in Fig. 2.

A 3-way ANOVA with 2 repeated measures was used to determine main effects for schedule conditions, order of presentation and days, and interactions between them.

No significant main effects were found between the infusion rates of animals in schedule conditions, between order of presentation, or over days. There were also no significant interactions. These results suggest that reversing schedule and no schedule conditions does not significantly alter the rate of cocaine self-administration.

The patterns of cocaine self-administration found in this, and in the previous experiment, do not conform to those found using other drugs within this paradigm [7, 8, 9, 10, 13]. It would appear that the operation of an FT-1 food delivery schedule plays no major role in the self-administration of cocaine at the dose explored.

## GENERAL DISCUSSION

The findings from the present experiment confirm that doses of cocaine known to be too low to initiate or maintain responding in rats at free feeding body weight [11,12] are self-administered at significant levels by animals reduced to 80% body weight. This finding supports that of Carroll *et al.* [2], and suggests that stimulant self-administration is enhanced by manipulating physiological factors.

It is of interest to note that patterns of responding observed in the present experiments are characteristic of patterns commonly reported by other investigators [3, 6, 11, 13, 14, 16]. These patterns included rapid acquisition of drug self-administration; erratic alternating days of high low drug intake; and large individual differences in amounts of drug self-administered by individual animals.

Another finding of interest was that the operation of an FT-1 schedule did not significantly enhance or inhibit drug intake, irrespective of the animals' nutritional state. The failure to find a significant increase in the self-administration rates of free feeding body weight animals in the presence of a schedule is not, however, of major consequence. Investigations of other drugs under these conditions have yielded similar findings [10]. Moreover, investigations of schedule induced behaviors generally indicate that the intensity of these behaviors is closely related to body weight reductions [15].

The finding of consequence, however, was that the operation of an FT-1 schedule did not significantly affect self-administration rates of reduced body weight animals. This pattern of responding has not previously been reported with either similar, [13] or different [8, 9, 10] classes of drugs within this paradigm. Whilst it is not surprising that under a given set of conditions, drugs from different classes will result in dissimilar patterns of responding, [14] it is anticipated that drugs from the same class should be self-administered in similar patterns. As shown, this was not the case. In the presence of an FT-1 schedule, the pattern of cocaine self-administration by reduced body weight animals was dissimilar to that found with d-amphetamine reinforced animals under similar conditions. Although the explanation for this difference is not clear, it was suggested by Takahashi *et al.* [13] that the three way interaction between d-amphetamine, physiological factors and schedule conditions gave rise to a 'differential sensitivity' to the pharmacological properties of the drug, which inhibited drug intake. In the present investigations, no such interaction appeared to occur to any significant degree. In fact, the operation of an FT-1 schedule was largely irrelevant to the drug taking response.

In conclusion, the results of the present investigation with cocaine, and the results of Takahashi *et al.* [13] with d-amphetamine, indicate that stimulant self-administration is considerably amplified under conditions of food deprivation. Support for this contention has recently been provided by Carroll *et al.* [2] who also reported large increases in low dose cocaine self-administration under conditions of food deprivation. Although more extensive investigations need to be undertaken before any firm conclusions can be reached, these findings, collectively, lead to the suggestion that the clinical use of stimulant type anorectics in the treatment of obesity may well place the patient 'at risk' for drug dependence.

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